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Published by Oxford University Press on behalf of the International Epidemiological Association *International Journal of Epidemiology* 2012;**41**:1072–1075

doi:10.1093/ije/dys076

Commentary: Lifestyle factors and colorectal cancer microsatellite instability—molecular pathological epidemiology science, based on unique tumour principle

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Accepted 16 April 2012

Colorectal cancer encompasses fundamentally heterogeneous multifactorial diseases,[1–3] as do breast, lung and other common cancers. Each tumour is unique in terms of the tumour microenvironment, interactome and intra-tumour heterogeneity, as well as host genomic variation and lifestyle and environmental exposures. There is likely a subtle difference in the local microenvironment even in a single organ system[4,5] or within a single tumour. This unique tumour concept is supported by technologies that have enabled reading whole genome, epigenome, transcriptome, etc. in human tumour specimens. Essentially, each tumour follows its own unique pathway of tumour evolution and progression,[6] and we classify tumours according to similarities in molecular signatures accumulated during the carcinogenesis process.[6] Accumulating evidence suggests that aetiological factors influence the carcinogenesis process differentially according to tumour pathway (hence, tumour classification).[2,3] Therefore, just as different tumours respond variably to therapy, causation appears to differ by tumour subtype. However, traditional cancer epidemiology approaches (including many genome-wide association studies) have not generally taken tumour heterogeneity into consideration or analysis.

Recently, molecular pathological epidemiology (MPE) has been established as a transdisciplinary field,[1–3] which examines a relationship between exposures and molecular signatures in tumour, as well as interactive influences of the exposures and molecular features on cancer progression.[7,8] MPE is philosophically based on the concept of the uniqueness and heterogeneity of neoplastic diseases. Through MPE research, we can refine risk estimates for specific subtypes, and gain pathogenic insights on how potential aetiological factors influence different carcinogenesis pathways.[1–3] MPE may uncover causal associations in tumour subtypes, which had been masked when all tumours in an anatomical site were pooled together.[2,3]

In this issue of *IJE*, utilizing the MPE approach, Hughes *et al*.[9] prospectively examined the relationship between anthropometric measurements and risk of colorectal cancer according to status of *BRAF* mutation and microsatellite instability (MSI). Notably, this study represents the first MPE study to conduct a pooled prospective analysis using geographically and operationally distinct cohort studies. One substantial challenge in MPE research is limited statistical power, because MPE research is essentially a subset analysis using tumour classification.[3] The strategy of pooling multiple cohorts may potentially alleviate this issue. Hughes *et al*.[9] successfully demonstrated that an increase in body mass index (BMI) was associated with increased risk of microsatellite stable (MSS) cancer but not of MSI-high cancer, although the risk difference was not statistically significant. These data are generally in agreement with the previous case–control studies.[10–12]

Energetics and inflammation have been implicated in colorectal carcinogenesis. Obesity was associated with CpG island methylator phenotype (CIMP)-low/negative colon cancer in a case–control study,[13] although in a case–cohort study, body size and physical activity were associated with colorectal cancer risk but not differentially by CIMP status.[14] Of note, in colorectal cancer, MSI-high is associated with CIMP-high, which is associated with *BRAF* mutation.[15–18] Thus, these molecular correlations can confound the apparent relationship between an exposure and a tumour variable. This 'tumour molecular confounding' is not typical confounding in an epidemiological sense because the nature of the relationships among molecular markers is not always understood. Recently, a prospective study of women showed that obesity was associated with colorectal cancer risk differentially by fatty acid synthase (FASN) expression.[19] FASN has been known to be physiologically regulated by energy metabolic status. FASN is implicated in carcinogenesis, and its expression is associated with MSI-high colorectal cancer, independent of CIMP status.[20] The apparent relationship between obesity and MSS cancer might be due to the link between obesity and FASN-negative tumour.[19] Therefore, the interrelationship between energetics and tumour molecular features seems complex and more investigations are needed in this area.

Hughes *et al*.[9] also showed that body height was associated with increased MSI-high (or *BRAF*-mutated) cancer risk to a significantly greater degree than MSS (or *BRAF*-wild-type) cancer risk. Body height may reflect exposure to energy metabolic status and hormonal milieu in the growth period. Interestingly, in the Netherlands Cohort Study, calorie restriction in early life might be associated with a lower risk of CIMP-high colorectal cancer.[21] Although confirmation by independent data sets is necessary, these data suggest that energy metabolic status in early life to adolescence may influence carcinogenesis pathway that involves epigenetic instability, whereas later in life, energy metabolism is more relevant to MSS or FASN-negative tumour development.

Although MPE appears to be a promising science,[2,3] as a largely observational endeavour it encompasses all limitations of observational epidemiology. In addition, there are specific caveats, which have been discussed in detail elsewhere.[3] We believe that MPE research should be conducted in a rigorous manner, so that findings can be generalized and appropriate public health measures can be taken based on new knowledge. To that end, we need to develop international guidelines for MPE, an extension of the STROBE (STrengthening the Reporting of OBservational Studies in Epidemiology) guidelines, which can be termed 'STROBE-MPE'.[22]

For centuries, organ-based cancer classification has been useful. However, we are now geared to enter an era towards more personalized treatment in medicine.

Epidemiologists should also regard each tumour as unique, and use molecular classification to better design epidemiology studies. Eventually, population cancer registries worldwide should record classification based on molecular pathogenesis and disease heterogeneity, which will accelerate the advancement of population health science. To advance the integrated interdisciplinary field of MPE, there is great need to educate epidemiologists in molecular pathology, as well as great need to educate pathologists in epidemiology and biostatistics.[22] We believe that MPE can serve as a successful platform for such an interdisciplinary integration of diverse fields.

In summary, the study by Hughes *et al*.[9] underscores the importance of the MPE approach in our quest for cancer aetiologies as well as the potential of a strategy of pooling multiple studies to overcome challenges and gain generalizable knowledge. In addition, to increase statistical power of individual population-based MPE studies, cooperation of all hospitals and pathology laboratories in provision of medical information and biospecimens is crucial. We genuinely call for collaboration and cooperation for the advancement of population science and public health.

Funding

US National Institute of Health [R01 CA151993, to S.O.; P01 CA87969, to S.E. Hankinson; P01 CA55075, to W.C. Willett].

Acknowledgements

The content is solely the responsibility of the authors and does not necessarily represent the official views of US National Institute of Health.

Conflict of interest: None declared.

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